REMARKS

This case, as-filed, contained claims 1-50. Claims 2-11, 18, 29, 30, 37, 42-45 and 47-50 have been withdrawn from consideration as directed to a non-elected invention. Claims 1, 12-17, 19-28, 31-36 and 46 were rejected. This amendment cancels claims 2-11, 18, 29, 30, 37, 42-45 and 47-50 as directed to a non-elected invention. In addition claims 1, 14, 17, 19, 20, 24 and 46 have been canceled. Claims 12, 13, 21, 23, 25, 26, 28, and 32-36 have been amended. New claims 51-62 have been added. Claims 12, 13, 15, 16, 21-23, 25-28, 31-36 and 51-62 are now in this case.

Amendment of the Claims

Claim 12 has been amended to recite that the translocating polypeptide exhibits receptor-independent and energy-free penetration of cell membranes, that the cell does not have a cell wall; and that the one or more regulatory agents include a recombinase. Additionally, the phrase "a cell in culture" has been rewritten simply as "a cell." The amendment is supported in the specification on page 2, lines 2 and 28 and on page 6, lines 14-15.

Claim 21 has been written in independent form reciting that the translocating polypeptide exhibits receptor-independent and energy-free penetration of cell membranes; that the cell does not have a cell wall; and the one or more regulatory-agents include a polymerase specific for the promoter. The amended claim is supported by original claims 12 and 21 and in the specification on page 6, lines 14-15.

Claim 23 has been written in independent form reciting that the translocating polypeptide exhibits receptor-independent and energy-free penetration of cell membranes, that the cell does not have a cell wall; and the one or more regulatory-agents include an HIV Rev protein and the one or more regulatory elements the HIV Rev response element (RRE). The amended claim is supported by original claims 12 and 23 and in the specification on page 6, lines 14-15.

Claim 13 is amended to specify that the cells can be mammalian, yeast or insect cells.

Claims 25, 26, 28 and 31 have been amended to recite "one or more regulatory agents" for consistency with the original language of claim 12 from which they depend.

Claim 32 has been amended for improved consistency with the language of claim 12 from which it depends, to improve its clarity and to better claim the invention. The phrase "one or more regulatory agents" is consistent with the language of claim 12. The use of the phrases "a first nucleic acid with at least one site-specific genomic recombination site" and a "second nucleic acid containing the target gene and at least one site-specific-recombination site" are believed to more clearly claim Applicant's method. The claim further recites that "the recombinase is specific for the-recombination sites" in the first and in the second nucleic acid and that translocation of the site-specific recombinase causes recombination between the site-specific recombination sites "resulting in stable integration of the target gene into the genome of the cell at the genomic recombination site." The amendments to the claim are supported by the original claim and through out the specification, particularly at pages 22 and 23.

Claim 35 has been amended for improved consistency with the language of claim 12 from which it depends, to improve its clarity and to better claim the invention. The claim now specifies that the one or more regulatory elements are flanked by site-specific recombination sites. Further, the phrase "one or more regulatory agents" has been added for consistency with claim 12. Note that at page 22, lines 21-22, the specification states that a pair of recombination sites can be placed to flank a polynucleotide segment to be excised. Throughout the specification, the regulatory agents, which include recombinases, are stated generically to be useful for modulating target gene expression by their action on regulatory elements. Thus, the specification taken as a whole described the use of recombinases to excise polynucleotide sequences (containing regulatory elements) to modulate target gene expression.

The new claims are fully supported by the original claims and the specification as filed. Claim 51 is supported by recitations in the specification, for example, at page 8, line 15. Claim 52 is supported by recitations in the specification, for example, at page 27, lines 17-18. Claim 53 is supported by recitations in the specification, for example, at page 18, lines 27-30. Claims 54 and 55 are supported by recitations in the specification at pages 19-21.

Claim 56 is an independent method claim similar to claim 12, but reciting that the one or more regulatory agents include a DNA-binding protein. The claim also recites that the translocating polypeptide exhibits receptor-independent and energy-free penetration of cell membranes, and that the cell does not have a cell wall. The claim is supported, for example, on page 15 starting at about line 19.

Claim 57 is supported, for example, in the specification at page 15, lines 22-23. Claim 58 is supported on page 17, lines 15-25 and page 18, lines 9-12, for example. Claim 59 is supported, for example, in the specification on page 16-17, bridging paragraph and sequence and in sequence ID No. 4. Claim 60 is supported in the specification, for example, on page 11, lines 13-15. Claim 61 is supported, for example, in the specification at page 12. Claim 62 is supported, for example, in the specification on page 16, lines 4-8.

None of the amendments to the claims or the new claims represent the addition of new matter.

Amendment of the Specification

The Specification has been amended to include on page 1 a cross-reference to related applications to complete formalities for making the priority claim

The Specification has been amended on pages 5, 6, 12, 13 and 28 to delete reference to Figures 6A, 6B, 8A and 8B and to amend the reference to Figure 7 so that the text now refers to Figure 6. This amendment makes the text of the Specification

consistent with the amendment of the Drawings. In addition, a clerical error in the paragraph on page 28 has been corrected by the addition of a period at the end of the last sentence of the paragraph.

Several clerical errors in bibliographic references on pages 2 and 13 have been corrected.

None of the amendments to the specification represents the addition of new matter.

Amendment of the Drawings

Applicant has requested approval of an amendment of the drawings as filed in the International Application from which this application under 35 U.S.C.§371 derives. Applicant requests that original Figures 6A, 6B, 8A and 8B which are nucleotide sequences be canceled and deleted as redundant over the pages of sequence listing that have been added to the specification. Applicant also requests that original Figure 7 be relabeled Figure 6. Applicants have also made formal changes to the drawings to comply with PTO form 948. Formal replacement drawings are submitted herewith which include the requested changes. The amendments to the drawings do not represent the addition of new matter.

The Rejections

Claims 1,12-14, 17, 19-28, 31-36, 38-41 and 46 are rejected under 35 U.S.C. 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey possession thereof at the time of filing to one of ordinary skill in the art. Applicant respectfully traverses this rejection with respect to the claims as amended.

The Examiner alleges that the "translocating polypeptide" is a critical element in the claimed method that is not adequately described in the specification. Refering to Falnes et al. 2001, Schwarze and Dowdy, 2000 and Schwarze et al 2000. the Examiner

states that "the structural characteristics that confer upon a peptide or protein the properties of" a translocating polypeptide were not known at the time of filing, that "structural comparisons between known [protein transduction domains] provide little insight into the mechanism of transduction," and that the "mechanism of cellular targeting or membrane penetration" by such proteins are not known. The Examiner alleges that in view of the lack of structural and mechanistic information about translocating polypeptides that Applicant's specific description of three distinct translocating polypeptides is not sufficient to provide an adequate description.

To emphasize unique art-recognized characteristics of "translocating polypeptides" claim 12 has been amended to specifically incorporate functional properties of the translocating polypeptides recited on page 2 and page 6 of the specification that the translocating polypeptides exhibit receptor-independent and energy-free penetration of cell membranes. All claims remaining in this case depend from claim 12 or contain the same recitations of functional properties of the translocating polypeptides. Applicant notes that original claims 15 and 16 which have not been amended were considered by the Examiner to satisfy the written description requirement

The Examiner's narrow focus on the structure of translocating polypeptides and the mechanism by which they function is misplaced. The published Written Description Guidelines (page 8) indicate that in analysis of adequate description of a genus that a range of identifying characteristics should be considered including "partial structures, physical-chemical properties, functional characteristics, known or disclosed correlations between structure and function and method of making." Further, the adequacy of the written description of a patent application is to be viewed through the eyes of one of ordinary skill in the art. When employing this standard it is necessary to consider what is generally known in the art about the materials described in the application.

The "translocating polypeptides" of the claims as further characterized by the unique characteristics defines a genus of polypeptides unified by common function. The specification describes representative members of the genus that were known at the time

of Applicant's filing. As summarized in Table 1 of Schwarze et al. Trends in Cell Biology vol. 10, July 2000 referring to references 1-4 (all dated in 1997 or earlier) amino acid sequences characteristic of TAT, VP22 and Antp (designated protein transduction domains: PTD) were known in the art at the time the application was filed. Applicant also noted in the specification published PCT application WO 97/05265 published Feb. 13, 1997 which provides HSVI VP22 sequence and the sequences of homologs of VP22 from other herpes viruses. The structural information known in the art at the time of filing in combination with the descriptions in the specification would allow the identification and isolation of translocating polypeptides in addition to those known in the art at that time..

The commonality of function of translocating polypeptides is emphasized in the specification and the enumerated properties would have been recognized by one of ordinary skill in the art at the time the specification was filed to distinguish a genus of related polypeptides. It is clear based on the content of several review articles published within about a year of Applicant's filing date that the art at the time of Applicant's filing did recognized the relatedness of these peptides (represented by TAT, VP22, Antp and Protein H). See Schwarze and Dowdy, Schwarze et al. and Schwartz and Zhang "Peptide-Mediated Cellular Delivery" Current Opinion Molecular Therapeutics 2(2):162-167 (2000) (now of record.)

The description in the specification of the genus of "translocating polypeptides" is adequate because (1) the translocating polypeptides as described and claimed are related by unique functions (receptor-independent penetration of cell membranes, and energy-free penetration of cell membranes); (2) at least four different species of translocating polypeptides had been identified (in the art) at the time of Applicant's filing and Applicant's specification specifically identifies three of the known translocating polypeptides which exhibit these functional characteristics; (3) methods were known in the art at the time this application was filed, based on these identifying functional characteristics, for identifying and isolating other species of this genus and (4) the structures of at least three of the translocating polypeptides were known in the art at

Applicant's filing date. The functional and structural descriptions in the specification in combination with what was known in the art at the time of filing about translocating polypeptides would have identified the functionally related genus of translocating polypeptides to one of ordinary skill in the art and would have indicated to that person that Applicant was in possession of the invention with respect to the use of that recognized genus of polypeptides.

The Office Action stresses that the mechanism by which translocating polypeptides function is unknown. However, it is clear that it is not necessary to understand this mechanism to employ the translocating polypeptides as demonstrated by the specific examples in the specification successfully employing such polypeptides and by reports such as those of Falnes and Phalen (both cited by the Examiner) which employ such polypeptides. Applicant's note that the Written Description Guidelines do not indicate that knowledge of mechanism is required to provide an adequate written description. The Office Action alleges that without knowledge correlating structure and function, one of ordinary skill in the art would not be able to recognize a translocating polypeptide by its structure. Applicant submits that one of ordinary skill in the art would recognize (and in fact does recognize) a translocating polypeptide by unique functional characteristics.

Applicant stresses that the claims are directed to methods which employ translocating polypeptides. The peptides themselves are not claimed and as indicated in the specification translocating polypeptides were known in the art prior to Applicant's invention. Thus, an adequate written description does not require structures or sequences of the translocating polypeptides.

In view of the forgoing, the specific description and examples provided in the specification in combination with the recognition in the art of a genus of functionally related polypeptides exhibiting receptor-independent and energy-free penetration of cell membranes (as now claimed) provide an adequate written description of the genus of translocating polypeptides. This rejection should be withdrawn.

Claims 1, 12-17, 19-28, 31-36, 38-41 and 46 have been rejected under 35 U.S.C. 112, first paragraph allegedly for lack of enablement. Applicants respectfully traverse this rejection with respect to the claims as amended.

The Office Action alleges that the specification is enable only for methods in which the "cell is not enclosed within a cell wall," the translocating polypeptide is "Vp22 polypeptide, Antp or Protein H," and the regulatory agent is "T7 RNA polymerase, HIV Rev protein, rhoA or Flp."

All of the remaining claims have been amended to recite that the cell in which target gene expression is to be modulated is a cell which "does not have a cell wall." This amendment obviates the rejection with respect to the scope of cells that can be employed in the claimed method.

Claim 12 and claims dependent there from have been amended to recite that the "one or more regulatory agents include a recombinase." This amendment obviates the rejection of claim 12 and claims that depend there from with respect to the scope of the regulatory agents that can be employed in the method.

Claim 23 has been amended to recite that the "one or more regulatory agents include an HIV Rev protein and the one or more regulatory elements include the HIV Rev response element (RRE)." This amendment obviates the rejection of this claim with respect to the scope of regulatory agents that can be employed in the method.

Claim 21 has been amended to recite that the "one or more regulatory agents include a polymerase." The specification specifically exemplifies a method of regulating target gene expression employing T7 polymerase. There is no reasoning on the record indicating that a given polymerases would behave or function differently in Applicants method than other polymerases. In the absence of such a showing, the demonstration of the method employing T7 polymerase is sufficient to demonstrate enablement of all

polymerases. The rejection of claim 21 should be withdrawn with respect to the scope of the regulatory agents that can be employed in the method.

The Office Action alleges that at the time of Applicant's filing it was not possible to possess or make a translocating polypeptide without empirical experimentation. As noted above, as evidenced by several review articles appearing within about a year of Applicant's filing date and referring to articles published before Applicant's filing date, translocating polypeptides were known in the art and several had been successfully employed for delivery of molecules (PNA's, or antisense oligomers) to cells. Those of ordinary skill in the art knew of several translocating polypeptides and could identify additional translocating polypeptides by assaying for their common functional features. Further, Applicant provides at least one method in Example 10 for determining whether a given translocating polypeptide fusion would enter a given cell. A patent application must provide a disclosure that allows one of ordinary skill in the art to practice the invention as claimed with undue experimentation. The fact that some experimentation might be required to practice the invention does not mean that the disclosure is not enabling. Enablement may be adequate even if the amount of experimentation required is voluminous, so long as there is sufficient guidance in the specification or known in the art as to how the experimentation should be conducted.

Applicant submits that in view of what was known in the art about already identified translocating polypeptides, the description and disclosure in the specification and the availability of methods for identifying translocating polypeptides that one of ordinary skill in the art could practice the invention with any translocating polypeptide sharing the unique functional characteristics now claimed.

In support of this rejection the Office Action indicates that there is unpredictability in the practice of this invention with respect to size limitations of what can be delivered by translocating polypeptides and the possible denaturation of proteins in the process of transduction. As a first matter, Applicant notes that the claims remaining in this case are not directed to any and all "cell process-modifying molecules."

Claims are directed to regulatory agents that are recombinases (claim 12 and dependents), polymerases (claim 21 and dependants), HIV Rev protein (claim 23) and DNA-binding proteins (claim 56 and dependents.)

With respect to size limitations of what can be successfully delivered by a given translocating polypeptide, one of ordinary skill in the art knows that such size limitations can occur with some translocating polypeptides, but also knows that other translocating polypeptides do not exhibit such limits. One or ordinary skill in the art knows (in view of the literature reports) either how to select a translocating polypeptide to deliver the size of protein needed or in the case where a size limitation has not been determined knows how to test whether or not a given translocating polypeptide will deliver a protein of a given size. Experiments to determine size limitations of delivery have been successfully performed in the art and there is sufficient guidance in the specification and in the pertinent literature to guide one of ordinary skill in the art to conduct similar experiments with any translocating polypeptide. As noted above, a claimed method may be enabled even if a large amount of experimentation is required so long as there is sufficient guidance as to how to conduct that experimentation.

With respect to the possible denaturation of proteins on transduction into cells, one of ordinary skill in the art knows that proteins may be denatured on transduction using translocating polypeptides, but also knows that other proteins or translocating polypeptides will not exhibit denaturation. One or ordinary skill in the art knows (in view of the literature reports) knows how to test whether or not a given protein will be denatured. Experiments to assess denaturation on delivery have been successfully performed in the art and there is sufficient guidance in the specification and in the pertinent literature to guide one of ordinary skill in the art to conduct similar experiments with a selected protein. As noted above, a claimed method may be enabled even if a large amount of experimentation is required so long as there is sufficient guidance as to how to conduct that experimentation. Thus, one of ordinary skill in the art can determine with undue experimentation whether or not a given protein can be delivered by the claimed method without denaturation.

In view of the amendment to the claims and in view of the foregoing arguments, this rejection should be withdrawn with respect to the claims remaining in this case.

Claims 32-35 are rejected under 35 U.S.C. 112, first paragraph for lack of enablement. The Office Action alleges that it would be undue experimentation to identify a cell line with a single recombination site or to generate a cell line in which all but one recombination site had been eliminated from the genome. Applicant respectfully traverses this rejection with respect to the claims as amended.

Claims 32 and 35 have been amended to recite "site-specific" recombinases and site-specific recombination sites. To the extent that this rejection was based on the interpretation of the claims as directed to generalized recombination, the rejection should be withdrawn. Applicant notes that the rejection is supported by reference to Lewin in Genes III (1987) which is described as teaching that "generalized recombination" can employ "any pair of homologous sequences." Claims 32-35 have been amended to clarify and emphasize that the claimed methods employ site-specific recombination by site-specific recombinases.

With respect to claims directed to the use of "site-specific" recombinases, the Office Action refers to Silver et al. U.S. published application 2002/0062489 paragraphs 0030 and 0031 for the teaching that it is likely that mammalian genomes contain a number of endogenous sequences that can function as targets for cre. Applicant notes that the specification of the published application merely states that one possible explanation of damage observed is the presence of multiple sites that can be cleaved by cre. The number of sites that actually can be cut by cre is not determined.

Claim 32 has been amended to replace "single genomic recombination site" with "at least one site-specific recombination site." Applicants note that claim 35 does not (and never did) recite the presence of a single genomic recombination site. Claim 32 as amended and claim 35 as filed do not require the presence of a single genomic recombination site. Thus, the rejection should be withdrawn to the extent that it relates to

the presence of such a required element. Practice of the invention as claimed does not require the identification of a cell line containing a single genomic recombination site. Thus, there is no issue with respect to the expense of undue experimentation in obtaining such a cell line.

In view of the forgoing this rejection should be withdrawn.

Claim 46 was rejected under 35 U.S.C. 112, second paragraph as indefinite. Claim 46 has been canceled and the term "refractory" which was objected to has not been used in the remaining claims. This rejection should be withdrawn.

Claims 1, 12-15, 17, 25-27, and 46 are rejected under 35 U.S.C.§102 as anticipated by Pooga et al. Pooga et al. relates to attachment of a peptide nucleic acid to Antp into a cell to regulate expression of the human galanin receptor.

Claims 1, 14, 17, and 46 have been canceled. Claim 12 and all claims that depend from claim 12 have been amended to recite that the one or more regulatory agents include a recombinase. Pooga et al. do not teach or suggest the use of a recombinase as a regulatory agent. The claims as amended should be considered patentable over the cited reference.

New claim 56 and claims that depend there from include the recitation that the one or more regulatory agents include a DNA-binding protein. Pooga et al. do not teach or suggest the use of a DNA-binding protein as a regulatory agent. New claim 56 and its dependent claims should be considered patentable over Pooga et al.

Claims 1, 2-17, 19, 20, 24, 25, 28, 40 and 46 are rejected under 35 U.S.C.§102 as anticipated over Phelan et al. which relates to a method for intercellular delivery of functional p53 by the VP22. Claims 1, 14, 17, 19, 20, 24 and 46 have been canceled. Claim 12 and all claims depending there from have been amended to recite that the one or more regulatory agents include a recombinase. Phelan et al. does not teach or suggest the

delivery of a regulatory agent that is a recombinase. Claim 12 and its dependent claims should be considered patentable over Phelan et al.

New claim 56 and claims that depend there from include the recitation that the one or more regulatory agents include a DNA-binding protein. Phelan et al. does not teach or suggest delivery of a DNA-binding protein employing a translocating polypeptide New claim 56 and its dependent claims should be considered patentable over Phelan et al.

Claims 12 and 40 are rejected over Phelan et al. as evidenced by Schuler and Green. Schuler and Green are cited to indicate that p53 responsive genes include those which generate toxic proteins. In view of the amendment of claim 12 to recite that the regulatory agent is a recombinase the teachings of Schuler and Green are not relevant. Phelan et al. even when viewed in the light of the teachings of Schuler and Green does not teach or suggest the delivery of a recombinase to a cell. Claims 12 and 40 as amended should be considered patentable over Phelan et al.

Claims 1, 12-15, 17, 25-27 and 46 are rejected under 35 U.S.C.§102 as anticipated by Allinquant et al. Allinquant et al. relates to delivery of antisense oligonucleotide to block expression of APP.

Claims 1, 14, 17, 24 and 46 have been canceled. Claim 12 and the claims that depend from claim 12 have been amended to recite that the one or more regulatory agents include a recombinase. Allinquant et al. does not teach or suggest the delivery of recombinase to regulate target gene expression.

New claim 56 recites that the one or more regulatory agents include a DNA-binding protein. Allinquant et al. do not teach or suggest the delivery of a DNA-binding protein employing a translocating polypeptide. New claim 56 and claims that depend there from should be considered patentable over Allinquant et al.

Claim 1 was rejected under 35 U.S.C.§102 as anticipated by Lissy et al. Claim 1 has been canceled obviating this rejection.

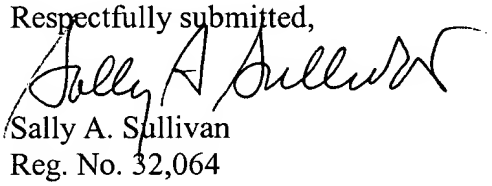
Lissy et al. relates to delivery of a Tat fusion with human papillomavirus E7 protein to modulate pRB activity in the cell. New claim 56 recites that the one or more regulatory agents include a DNA-binding protein. Lissy et al. do not teach or suggest the delivery of a DNA-binding protein employing a translocating polypeptide. New claim 56 and claims that depend there from should be considered patentable over Lissy et al.

In view of all the forgoing, the prior art rejections of the claims as amended should be withdrawn.

Conclusions

The claims as amended are believed to overcome the rejections. Passage to issue is respectfully requested. The application as filed contained 50 total claims of which three were independent. The application as amended contains 29 total claims of which three are independent. No fees for excess claims are believed to be due. This amendment is accompanied by an Information Disclosure Statement. A fee of $180.00 for submission of that statement is also submitted. The amendment is also accompanied by a Petition for Extension of Time of Three Months with appropriate fee ($930.00). If the fees submitted herewith are incorrect please deduct any deficiency or credit any overpayment to deposit account 07-1969.

Respectfully submitted,



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